

Perioperative Anaphylaxis

Aleena Banerji, MD
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San Diego, California

Objectives

- Better understand the differential diagnosis of perioperative anaphylaxis
- Evaluate and manage patients with a history of perioperative anaphylaxis
- Advise patients with a history of perioperative anaphylaxis that need to return to the operating room



Case Presentation

- 28 year old female
- No significant past medical history
- Elective laparoscopic cholecystectomy 6 months ago
- No previous exposure to anesthesia
- No known drug allergies



Patient with History of Perioperative Anaphylaxis

- Received a dose of cefazolin preoperatively
- Received midazolam, fentanyl, propofol, lidocaine, and rocuronium during procedure
- Developed significant hypotension 10 minutes after start of procedure
- No rash, hives or angioedema documented
- Hypotension responded immediately to treatment with epinephrine and benadryl
- Stable in recovery room with no other symptoms



Perioperative Anaphylaxis

- Anaphylaxis during surgical procedures is difficult to evaluate because of the rapid, successive use of multiple agents
- Careful analysis of anesthesia records is critical to a complete and thorough evaluation

Epidemiology: Anaphylaxis to General Anesthesia

- Incidence ranges from 1:3500 to 1:20,000
 - Most published reports are from studies in France, Australia, England and New Zealand
- Mortality ranges from 3-6%
- An additional 2% of patients experience significant brain damage

Murat et al, 1999; Fisher et al., 1993;
Currie et al., 1993; Mitsuhashi et al., 1992

Differential diagnosis of perioperative anaphylaxis

Table 1

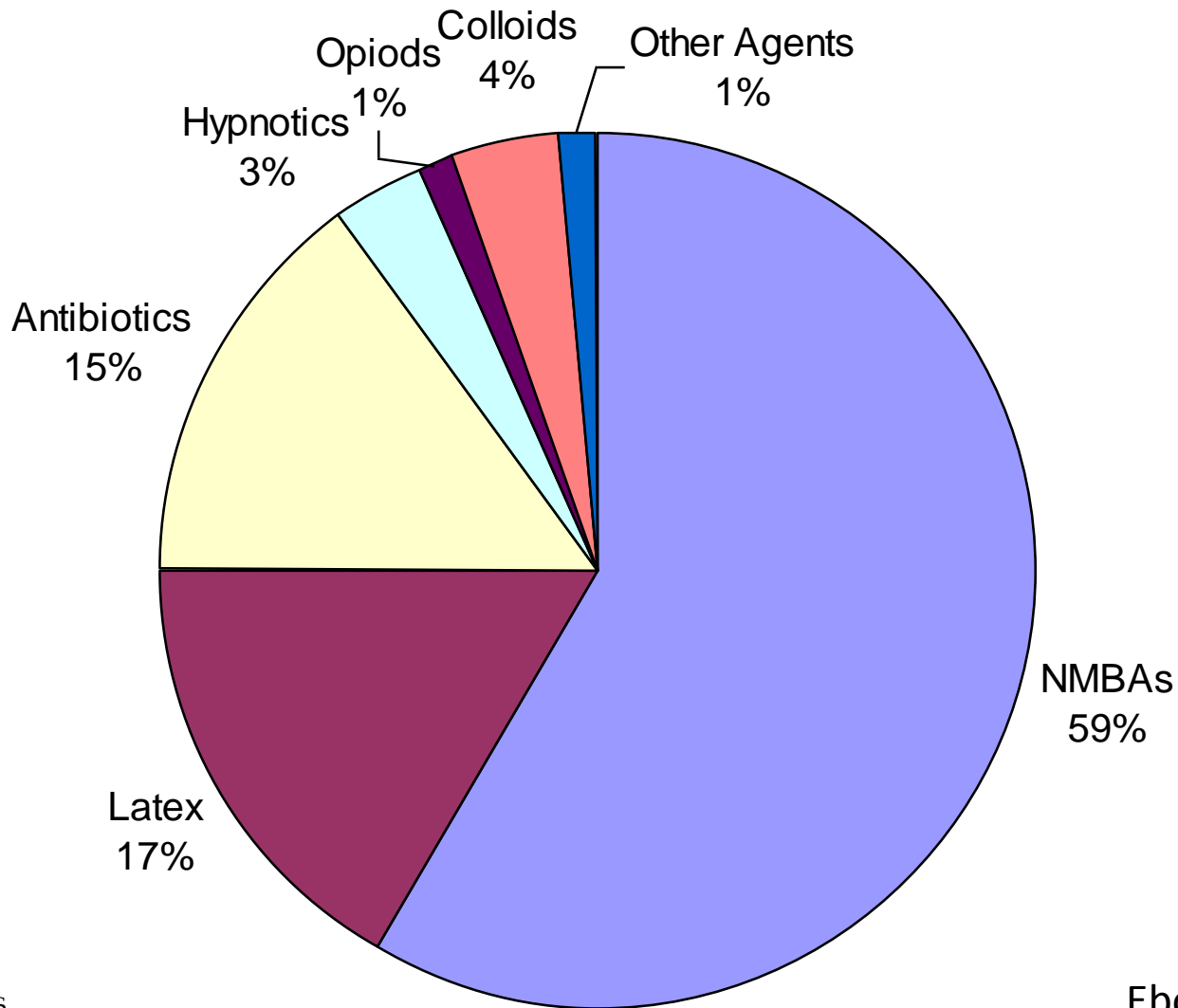
Differential diagnosis of anaphylaxis during anesthesia

Drug overdose and interactions
Cardiac/vascular drug effects
Asthma
Arrhythmia
Myocardial infarction
Pericardial tamponade
Pulmonary edema
Pulmonary embolism
Tension pneumothorax
Hemorrhagic shock
Venous embolism
Sepsis
C1 esterase inhibitor deficiency
Mastocytosis
Malignant hyperthermia (succinylcholine)
Myotonias and masseter spasm (succinylcholine)
Hyperkalemia (succinylcholine)

Differential Diagnosis

- Neuromuscular Blocking Agents
- Latex
- Antibiotics (b-lactams)
- Hypnotics (propofol, thiopental)
- Opiates
- Aspirin and NSAIDs
- Colloids
- Chlorhexidine and other antiseptics
- Local Anesthetics
- Protamine and Heparin
- Dyes (Methylene Blue)
- Oxytocin
- Aprotinin

Etiology of Perioperative Anaphylaxis



Ebo et al., 2007

Risk Factors

- Female
- Atopy (not for NMBAAs)
- Prior history of anaphylaxis
- Prior history of drug allergy
- History of multiple prior procedures



Predisposing Factors by History

- Spina Bifida → Latex Allergy
- Health Care Workers with glove dermatitis → Latex Allergy
- Gelatin Allergy → Colloids
- Allergy to exotic fruit (kiwi, chestnut, mango, avocado, banana) → Latex Allergy

Evaluation

- History, History, History
 - Timing of administration of drug and onset of reaction



Clinical symptoms and reaction severity will not allow one to distinguish between an immune-mediated IgE reaction and an anaphylactoid reaction due to direct mast cell activation



Important Questions

- Was this a first dose reaction?
 - First dose reactions are not usually IgE mediated unless prior sensitization occurred
- What is the nature of the reaction?
 - Urticaria and angioedema vs. maculopapular rash
- What was the time course of the reaction?
 - Within minutes, hours or days

Time Elapsed between Administration and Onset of Symptoms

- 90% of cases, symptoms usually start within 5-10 minutes after intravenous administration of the responsible agent
- In contrast, anaphylaxis from latex and antiseptics (chlorhexidine) is usually 20-40 minutes later
 - Slower absorption through skin or other mucosal surfaces

Evaluation

- History, History, History
 - Timing of administration of drug and onset of reaction
- Caveats of skin testing
 - Not indicated for non-IgE mediated reactions
 - Often uninformative if negative
 - Must rule-out an irritant reaction if positive



What can an Allergist Provide?

GENERAL GUIDANCE BASED ON KNOWN INFORMATION

- Skin testing using non-irritating concentrations
 - NMBAAs
 - Antibiotics
 - Latex
 - Local Anesthetics
 - Propofol
 - Fentanyl
 - Clorhexidine
 - Protamine
 - Oxytocin



Allergy to NMBAs

- IgE antibodies to the two quaternary or tertiary ammonium ions mediate anaphylaxis
- Many OTC drugs, cosmetics, and food products contain quaternary or tertiary ammonium ions that can lead to sensitization
- Therefore, can often see reactions with *“first”* exposure to NMBAs

NMBAs (N=336)

- Rocuronium 29%
- Succinylcholine 23%
- Vecuronium 18%
- Mivacurium 18%
- Pancuronium 7%
- Cisatracurium 4%
- Atracurium 1%

Skin Testing Concentrations

Available Agents	Concentration (mg/mL)	SPT		IDT	
		Dilution	C _{max} (mg/mL)	Dilution	C _{max} (mg/mL)
NMBAs					
Atracurium	10	1/10	1	1/1 000	10
Cisatracurium	2	Undiluted	2	1/100	20
Mivacurium	2	1/10	0.2	1/1 000	2
Pancuronium	2	Undiluted	2	1/10	200
Rocuronium	10	Undiluted	10	1/200	50
Suxamethonium	50	1/5	10	1/500	100
Vecuronium	4	Undiluted	4	1/10	400

Latex Allergy

- Derived from the *Hevea brasiliensis* tree
- Universal precautions by the FDA in the 1980s in the setting of HIV led to a dramatic increase in the use of latex gloves
 - The high demand led to a decrease in manufacturing time and therefore increased protein content in gloves
- Latex allergy is decreasing due to increased awareness and avoidance
- High risk groups include health-care workers, patients with a history of multiple procedures



Latex Skin Testing Protocol

1. Soak a latex glove in saline for one hour and perform an epicutaneous test with the extract
2. If negative, apply a wet latex glove to the forearm for 30 minutes
3. If negative prick the skin through the wet latex glove

Antibiotics

- Penicillins and cephalosporins elicit approximately 70% of perioperative anaphylactic reactions to antibiotics
- Quinolones are the third most important group of antibiotics involved in perioperative anaphylaxis
- Bacitracin and rifamycin applied locally to irrigate wounds also can cause anaphylaxis



Antibiotic Skin Testing

Available Agents	Concentration (mg/mL)	SPT		IDT	
		Dilution	C _{max} (mg/mL)	Dilution	C _{max} (mg/mL)
Antibiotics					
PPL		Undiluted	0.035	Undiluted	35
MDM (penicillin)		Undiluted	1	Undiluted	1000
Penicillin G		Undiluted	20–25 × 10 ^{3,a}	Undiluted	20–25 × 10 ^{3,a}
AX, AMP		Undiluted	20–25	Undiluted	20–25 × 10 ³
Other penicillins					
Cephalosporins		Undiluted	1–2	Undiluted	1–2 × 10 ³
Vancomycin	500			1/5 × 10 ⁶	0.1
Gentamycin	40	Undiluted		1/10 ²	400

Value of Skin Testing

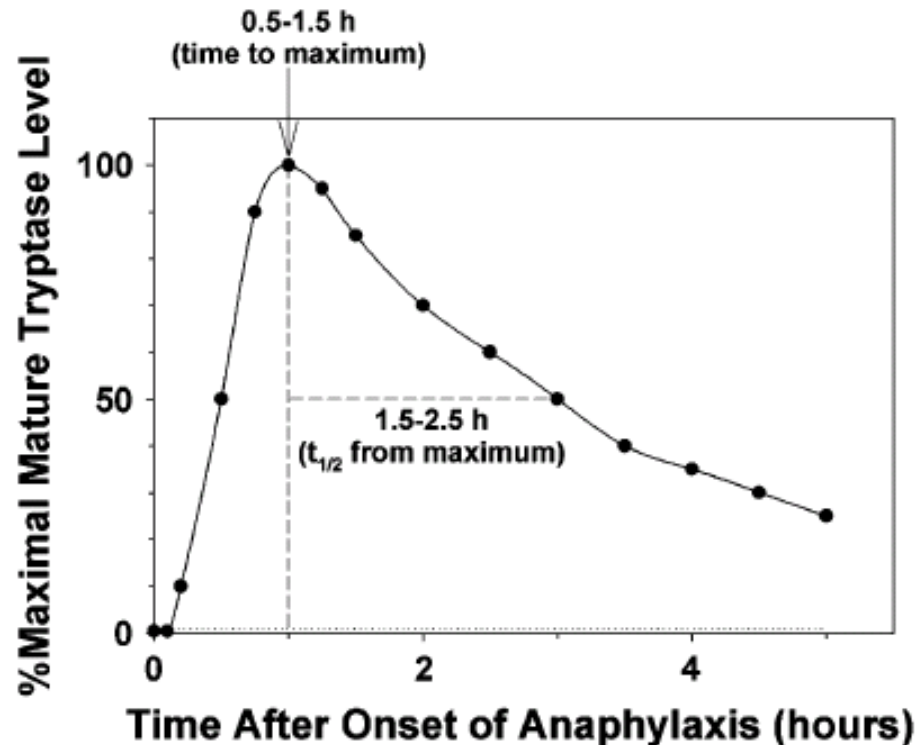
- NMBAAs
 - 60-70% cross-reactivity among agents
 - Literature suggests 80-90% sensitivity and specificity
- Latex
 - No standardized extract for skin testing available
 - RAST test 20% false negative rate
- Antibiotics
 - Lack of major and minor determinants
 - Use of non-irritating skin testing concentrations

Evaluation

- History, History, History
 - Timing of administration of drug and onset of reaction
- Caveats of skin testing
 - Not indicated for non-IgE-mediated reactions
 - Often uninformative if negative
 - Must rule-out an irritant reaction if positive
- Delay skin testing 4-6 weeks to avoid refractory period
- RAST testing often not available or sensitive/specific
- IgG, IgA and IgM to specific drugs are not useful
- Serum tryptase within 2-4 hours

Serum Tryptase Levels

- Half-life is approximately 120 minutes
- Tryptase level suggested within 4 hours of reaction



Tryptase

- Marker of mast cell activation
- Pro-tryptase (β) is constitutive and elevated in mastocytosis
- Total tryptase elevated with mast cell activation

Mature and total tryptase levels

Clinical condition	Tryptase levels (ng/mL)		Tryptase ratio (total/mature)
	Total	Mature	
Normal	1–15	<1	Not applicable
Systemic anaphylaxis (acute)	> Baseline	>1 ^a	<10
Systemic mastocytosis (nonacute)	>20 ^b	<1 to small elevations	>20

28 year old female with perioperative anaphylaxis

- Skin testing to midazolam, fentanyl, propofol, lidocaine, rocuronium and cefazolin was negative
- RAST Latex was negative
- Skin testing to all agents including latex was negative

Skin Testing is Negative: Next Steps?

- Comprehensive allergy evaluation is unable to identify causative agent
- Review differential diagnosis
- Create list of high vs. low likelihood agents responsible for perioperative anaphylaxis

Management

- Recommend an unrelated alternative medication
 - Most common approach
- Recommend a medication not identical to, but potentially cross-reactive with the drug in question
 - Low cross-reactivity between PCNs and cephalosporins
 - Significantly less with 3rd and 4th generation cephalosporins

What is the Value of Prophylaxis?

- No data exist in the current literature for standard prophylaxis prior to anesthesia
- Data exist for steroid and antihistamine prophylaxis for patients with IV contrast allergy
 - Mechanism of prophylaxis not well understood
 - Not IgE mediated
- Antihistamine prophylaxis may be helpful to reduce the incidence of adverse effects due to direct histamine release, but no data for anaphylaxis



Subsequent Anesthesia in Patients with Prior Anaphylaxis

- No subsequent anaphylaxis in 7 patients with negative skin testing (Thacker et al., 1999)
- 43 NMBA skin test positive patients, 19 had uneventful anesthesia with negative skin testing to NMBAs (Soetens et al., 2003)
- Evaluated 27 patients, no subsequent anaphylaxis in 3/11 with negative skin testing and 8/16 with positive skin testing that returned to the OR (Moscicki et al., 1990)



Conclusions

- Review the history, clinical symptoms, anesthesia record and consider differential diagnosis
- Comprehensive allergy evaluation is helpful in evaluation of perioperative anaphylaxis

